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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

SEPTEMBER 1940

THE PROBLEM OF AGING

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IT is remarkable that the problem of aging, one which has existed since the beginning of the human race, should have excited so little interest and been so largely neglected until recent times. Long before Cicero delivered his often quoted oration on Old Age, scholars exhibited a philosophical interest in the process of aging. Later, the pathological aspects of the subject excited some attention but the subject of old age as a far-reaching, vital problem of great medical, social and economic importance, has only aroused active discussion within the past decade.

The problem was of little general interest because until recently it could hardly be said to exist. A consideration of the changing trends in the age of the population, particularly of the western world, throws light on this question. This aspect of the problem of aging has been well discussed in the suggestive contribution of Louis I. Dublin in the admirable group of essays sponsored by the Josiah Macy Foundation in which are presented in a scholarly way, the biological and medical aspects of the aging process.

This subject involves a discussion of life span and life expectancy. The restricted and proper definition of life span is the limit of duration beyond which individual human life does not extend. It is almost impos-

sible to find accurate data based upon authentic records upon which to compute life span. Most authorities are in agreement that, in all probability, life span has varied little for many generations and that the one-hundred-year length of life is rarely exceeded by man.

In contradistinction to life span is life expectancy, which is computed from life tables from which may be reckoned the expectation of life at any age. As Dublin well puts it: "The life table shows what would be the number of survivors to successive ages, what would be the number of deaths at successive ages and what the expectation of life would be if the death rates at each age remained constant as of the calendar year or period for which it is constructed."

From a study of the life tables constructed for various periods, striking results may be obtained. It has been estimated that the mean length of life in the days of the Roman Republic was between 20 and 30 years. This life expectancy at the end of the 17th century had only advanced to 33.5 years. In a country such as Sweden between 1755 and 1776 the mean length of life was only 34.5 years. Life tables constructed for that country between 1816 and 1840 showed that life expectancy had only increased 7 years. From 1861 on, tables were constructed for successive 10-year periods. These showed a steady upward progress in life expectancy; from 44.6 years to 57 years for the period between 1911 and 1920 and during the next decade, the expectation of life had reached 62.3 years. In the early days of this Republic, a little more than a decade after the Declaration of Independence was signed, the mean length of life has been estimated to have been 35.5 years. From Massachusetts life tables in 1850, life expectancy had advanced to only 40 years. From the beginning of the 20th century on to the present, longevity in the United States has steadily advanced. In 1900 it was about 50 years. Twenty years later it had reached 55. The tables for 1930 show that it had passed 60 years and an analysis of the past decade unquestionably indicates a still further increase in the expectation of life.

There are certain basic factors which are largely responsible for the marked improvement in longevity that has taken place during the last half-century. A study of the figures makes it clear that this gain in life expectancy has been largely centered in the earlier years of life. In white males the expectation of life at birth in 1901 was 48.23 years; by 1931 this had been increased by 10.61 years. On the other hand, during the productive period of life which reaches its height at 40, the increase in

longevity was only 0.74 years and during the latter years of life, the gain that occurred was negligible. The situation with white females was essentially the same although the gains that occurred were slightly greater. It is reasonable, therefore, to conclude that this prolongation of life which is limited practically to the younger age groups, has been due to the control of those conditions that are known to be particularly destructive of youth. It is significant that this upturn in longevity took place coincidentally with advances in the control of the various infectious diseases, with the lessening of infant mortality and the awakening of the national conscience in matters pertaining to public health, sanitation and general improvement in living conditions. Coincidentally with the increase in life expectancy, has occurred a marked drop in the mortality rate over this same period, notably in the first 10 years of life, whereas the mortality rate in the higher age brackets varied but little. A consideration of the above figures makes it evident that during the last few years, the composition of our population from the standpoint of age has undergone a marked change and that we are rapidly becoming a nation of older people. Another factor that is bringing about an increase in our population of individuals of older age is the steadily declining birth rate. It is estimated that the birth rate in the United States in 1900 was 30 per 1,000; 15 years later it had fallen to 25 and it is said to be little if any over 16 per 1,000 at the present time.

A study of the age composition of the population of this country for the last 100 years further emphasizes this tendency to an increase in the older element of the population. In 1850, 52.5 per cent of the total population was under 20 years of age. Each census from then on showed that this percentage dropped. By 1900 it had fallen to 44.4. This had dropped by 1930 to 38.8 per cent and the most recent estimates indicate that only 36.7 per cent of the total population is under 20 years of age. Throughout these same periods, a proportionate increase has occurred among those aged 65 years or more. Less than 100 years ago they made up only 2.6 per cent of the total population. By 1930 this figure had doubled and it is now estimated that they make up about 6 per cent of the total population. During this period the percentage of the population aged between 20 and 40 years has remained virtually constant. The effect of these changes has been to bring about a startling increase in the number of older people, a situation fraught with far-reaching possibilities for our social, economic and political life. In short, the aging process with

its varied and perplexing problems has now become a vital issue in our national life.

Old age is essentially a biological problem. Its better understanding depends upon a clearer conception of the fundamental processes involved. Is aging to be regarded as a physiological involutionary phenomenon or is it disease? This differentiation is not easy and has challenged the best of philosophical and biological thought. The most logical scientific answer to this question is to be found in the delightful essay on Old Age written by the late Aldred Scott Warthin which was delivered in part before this Academy over a decade ago*. After pointing out that living organisms are destined to pass through the periods of evolution, maturity and involution, he shows that from the moment the ovum is fertilized throughout the entire period of development up to maturity, involutionary changes are taking place along with those of growth. In this way, structures that are no longer of service to the animal economy disappear. The tissue changes that are characteristic of these involutionary processes throughout life are in no way different from those that mark the involutionary changes of old age. From embryonic life until death, therefore, the processes of involution are active and at whatever period they are met and wherever encountered they are identical and consist of the following primary tissue changes:

1. Numerical atrophy—loss of power of cell division.
2. Quantitative atrophy—reduction in size and number of parenchymatous cells.
3. Shrinking and condensation of intercellular substance.
4. Vascular changes—vessel collapse and obliteration of lumen.

These are regarded by Warthin as the primary tissue changes of senescence; changes which are inherent in the organism, which are inevitable and physiologic and, if undisturbed by environmental factors or disease, ultimately lead to failure of vital functions and "biologic death." It is given to few individuals thus to die naturally, because upon these primary involutionary processes secondary pathologic conditions develop, the result of unfavorable environment or inherent cellular defects. These pathologic states have been grouped under changes secondary to vascular lesions such as thrombosis, embolism, hemorrhage, arteriosclerosis; those secondary to atrophy which causes functional failure of

* The Pathology of The Aging Process, *Bull. New York Acad. Med.*, 1928, *4:* 1006.

organs especially the endocrine and nervous system; and changes the result of stasis due to obstruction and resultant infection. It is these secondary conditions that lead to "pathologic death" which may occur at any period of life and which is usually responsible for preventing individuals attaining their life span.

The adoption of Warthin's conception not only furnishes one with a theory of old age based upon sound biologic principles but satisfactorily disposes of the many ingenious hypotheses that have been advanced to explain senescence as a progressive disease. For example, Brown-Séquard believed it to be due to vascular sclerosis; Victor Horsley held old age was the result of degeneration of the thyroid gland; while Lorand implicated all of the ductless glands. Metchnikoff's belief that intestinal putrefaction is the cause of old age has been widely discussed. Carrel undertook to explain the process on the basis of physiochemical changes in the blood serum which becomes senescent. In spite of the various mechanisms suggested, as Warthin has pointed out, these and other modern views on aging are fundamentally in agreement that old age is due to loss of growth energy on the part of the cells and when involution exceeds evolution, atrophies, both qualitative and quantitative, inevitably occur, with resulting functional failures.

Justification for an inquiry into the mechanism of aging is the desire to solve some of the inexplicable variations in the process that are encountered. It is a common observation that the rate of aging is inconstant and differs widely in individuals. There are those who before they reach 60, an age arbitrarily adopted by many students of the subject as the time when senescence may be said to begin, exhibit the physical and mental characteristics of advanced years. In contrast to these prematurely old, are individuals long past their biblical allotment of life who are conspicuous because of their vigor and alert mentality. Although admittedly in the minority, many outstanding examples may be cited of men and women whose old age was marked by their greatest creative achievements. Benjamin Franklin successfully directed the affairs of the State of Pennsylvania at 79. W. H. Welch, who lived to be 80, was active in medical education and research until he died. Goethe was 80 when he completed Faust. Between his 70th and 80th years, Thomas A. Edison introduced some of his greatest inventions. Elihu Root, who died at 98, was actively interested in public affairs after he was 90. Oliver Wendell Holmes began to write "Over the Tea Cups" at 80. At 98

Titian painted a masterpiece. Lord Balfour returned to an active political career at 72. Even after 85, Verdi wrote some of his best music. Innumerable similar instances could be drawn from the world's history. What is it that determines this variation in the rate and manifestations of aging? Heredity undoubtedly plays a prominent role. There are some who enter the declining years of life better endowed than others. Serious consideration, however, must be given to adequate nutrition in youth leading to optimal growth and development. Environmental factors such as fatigue, overwork, trauma, infections and intoxications leave their mark upon the individual. In addition to these biological aspects, social, cultural, economic and psychological influences are of an importance as yet not fully understood.

For the most part, the course of normal old age is modified by pathological changes and these in turn are largely the result of those diseases which fall within the category of the degenerative conditions, such as: chronic heart disease, chronic nephritis, arteriosclerosis, angina pectoris, cerebral hemorrhage, diabetes mellitus, cancer and numerous other conditions of like nature. Christian has pointed out that the diseases which play such an important role among older people thus far have been little if at all affected by the advances in preventive medicine and belong to the group of non-preventable diseases. A study of the principal causes of death during the past four decades shows that the rate per 100,000 for the non-preventable diseases has steadily risen, whereas there has been a striking mortality decline in preventable diseases. With this decline, has occurred an extension of life expectancy at birth which in 1800 was around 35 years, by 1900 had reached about 50 years and now is over 61 years. Further analysis shows that this increase in life expectancy is largely the result of eliminating preventable diseases among the younger age groups. In other words, preventive medicine has saved life chiefly among the young, thus enabling them to attain older years and become the victims of degenerative conditions in the end. In short, preventive medicine, by saving the young has materially increased the number of old people in our nation. This explains why heart disease, which was 4th among the causes of death in 1900, now holds first place; why cancer, which 40 years ago was 9th, is now 2nd; why nephritis has risen from 6th to 4th place; vascular cerebral lesions from 8th to 5th; diabetes mellitus from 19th to 10th. On the other hand, tuberculosis, which in 1900 was 1st, has dropped to 6th; diarrhea and enteritis have

fallen to 13th from 3rd; various infectious diseases such as pertussis, diphtheria, measles and typhoid have fallen from 16th, 10th, 14th and 11th places to 21st, 23rd, 24th and 25th respectively. Pneumonia and influenza in a period of 35 years have maintained the same relative positions as causes of death; namely, 3rd and 11th respectively. It is not too much to hope that with the recent advances in chemotherapy these infections heretofore so devastating will soon be found among the less common causes of death.

Although this downward shift in preventable diseases may justly be regarded as one of the triumphs of preventive medicine, it has also helped to bring about this relative increase in older people, who of necessity must suffer more from the degenerative diseases peculiar to later life. This change in the age composition of our population with its attendant increased incidence in the non-preventable diseases is bound to exert a marked influence on medical practice, assuming this trend continues, as in all likelihood it will.

Heretofore, physicians generally have been prone to regard too lightly the infirmities of age and have paid too little attention to disease as it manifests itself in the later decades of life. Such a tendency is not surprising in view of the widespread feeling that the degenerative diseases of the aged are as irremediable as they are inevitable. A changed attitude is essential if the medical needs of our ever-increasing older population are to be dealt with adequately in the future. In the past, the care and protection of youth has been our chief concern. With the steady conquest of an ever-increasing number of preventable diseases, medical care of the young will become less demanding, while correspondingly greater efforts will be required in the management of those who are older. In short, although the importance of pediatrics will not decrease, the importance of geriatrics inevitably must increase.

These changing conditions impose a new obligation upon all who are concerned with the training of physicians. Students should receive special training in geriatrics. They should be taught the altered ways in which diseases manifest themselves in older people. They should learn something of the problems of old age. They should be impressed by the fact that in the decades ahead, no inconsiderable part of their practice will be made up of older people whose special psychology and altered physiology must be understood.

In the future, pediatrics may become more restricted and deal more

with preventive medicine than with the actual treatment of disease. Ample opportunity will, nevertheless, be afforded physicians for the individual care of patients. There will not only be no dearth, but probably an actual increase in patients, the victims of degenerative processes, concerning which more needs to be learned and which provide fertile fields for biologic and medical research.

The symptomatology of the aged has not received the systematic study that it deserves. There are few careful clinical surveys that deal with any considerable group of older people. The most helpful records of complete group-studies on patients aged over 60 years come from the clinic of Dr. Lewellys F. Barker who, in conjunction with his associates, carried out a careful analysis of the more common symptoms of which elderly persons complain and the more outstanding abnormal physical findings in a group of 300 new patients over 60 years old. In this group, 240 were between 60 and 70 years of age. In those that were between 60 and 70, the chief complaints consisted in symptoms referable to: 1. Nervous system, 2. Digestive system, 3. Circulatory system, 4. Locomotor apparatus. There were relatively few whose outstanding symptoms suggested diseases of the respiratory system, the blood, the urogenital tract or the endocrines. In the group that was over 70 years of age, the initial complaints were not dissimilar to those of the younger group.

After these patients had been subjected to a thorough clinical and laboratory survey, a summary of the important diagnostic findings showed that in the age group between 60 and 70, diseases of the cardiovascular apparatus were the most common. The next in order of frequency were disorders of the nervous system, particularly those of a functional character. Diseases of the joints and bones, more especially osteoarthropathy furnished the next most frequent diagnoses. Contrary to what might be expected, in view of the large incidence of chief complaints which were referable to the digestive system, Barker and his associates found in this group only three cases of gall-bladder disease and two cases each of ulcer of the stomach and duodenum. Not surprisingly, oral sepsis was a fairly common finding. Other diagnoses made in this group included eleven cases of tumor, chiefly cancer, five cases of diabetes mellitus, five cases of lues and a few cases of obesity or undernutrition. In the older group of patients, relatively fewer severe maladies were found. Cardiovascular-renal disease was again predominant. The

incidence of cancer increased. Contrary to expectation, Barker found only four cases of senile psychoses in the entire group of 300 patients. In the main, the above analysis bears out the impression of most clinicians as to the distribution of the more serious diseases of the aged.

There is no more important aspect of senescence than the psychological and sociological ones. Old people present certain psychological phenomena peculiar unto them which must be thoroughly understood and appreciated if the problem of old age, both from an individual and a collective standpoint, is to be successfully handled. The prospect of old age does not appeal to most people. One's attitude towards growing old differs at various age periods. To the younger individual, the possibility receives scant consideration. In mature adult life, when old age is no longer remote, there are many who refuse to take a realistic view of the situation and shrink from all discussion of the problems of senility and death. It is not until the individual has actually attained old age that there is any degree of reconciliation to the restrictions of the advancing years and the relative proximity of death. Even then, there are many who are resentful of their infirmities and are unwilling to contemplate the inevitable with the calm philosophy that should characterize the psychology of the normal aged.

Those who have attempted to evaluate the view points of older people agree that it is not death that is feared by them so much as the dread of chronic invalidism and economic and social dependence—the thought of no longer being necessary and of losing a position of dominance whether that be in the family, industry or profession. A feeling of inadequacy may be said to be a prominent psychic burden of most old people. It is the common experience of every clinician that many older people suffer distressing unhappiness because of their unwillingness to accept their declining physical, mental and sexual powers with equanimity. They are reluctant to admit that age is robbing them of their ability to accomplish and to dominate as they formerly did and they try to blame their handicaps on failing health and various unfavorable environmental factors rather than on their declining years. Much of this psychology arises from the desire of people to regain their lost youth. They are not content with the prospect of a dignified, orderly, comfortable decline. Like Ponce de Leon of old, what they really seek is some "fountain of eternal youth." Hence, the abortive and ironical efforts at rejuvenation that from time to time have gained popularity in spite of

the fact that, viewed in the light of the pathology of old age, they are doomed to failure from the start. When we add to these psychological tribulations of growing old, the fear of economic insecurity, it is small wonder that senescence is not anticipated with enthusiasm.

Many of these factors so disturbing to the tranquility of the aged could be offset by the proper psychological handling of the individual. This brings the problem squarely before the physicians and immediate families responsible for the direction of the lives of the aged. Nothing is more disastrous or creates a worse psychic shock to aging people than a termination of their active interest. In all examples of successful and creative senescence to which reference has already been made, the common denominator is apparent; namely, a continuation of interest. When interest in some phase of life, be it profitable or otherwise, ceases, the burden of old age becomes heavier. For that reason, we, as physicians, should exercise our ingenuity in devising ways and means of keeping our older patients occupied. It is not sufficient to keep up the interest of the aged—what many seek most is a sympathetic understanding of their problem, particularly on the part of those with whom they live. The fact that an individual has undergone certain psychic changes, as the result of advancing years, does not alter the fact that he or she still is capable of emotional and sentimental reactions. Too often the needs of the aged in this respect are sadly neglected.

In spite of the trials which beset old age, it is not entirely without its compensations. To the healthy aged, especially if they can enjoy a certain financial independence, come freedom from responsibility and relief from the strain of competition. This brings increased leisure which enables them to pursue many activities and interests for which there was never time during their years of industrial or professional activity. They may live where and how they wish, no longer being forced to make their lives conform to the exigencies of their work. Long-neglected interest in cultural and civic problems may now receive their attention. The experiences gained in the course of an active life have adjusted their perspective and have given them mature judgment. Best of all, with aging has come conservatism. The prejudices and partisan fire of youth have given place to forbearance and tolerance. These are distinct assets, the views of the impetuous younger generation of our day notwithstanding—assets which should not be wasted but used and capitalized by Society, which with advantage might well hearken to the voice of experience.

There are definite political potentialities inherent in this conservatism of older people. The steady increase in the older group of our population has already been stressed. It is admitted that conservatism increases with age. As Professor John Dewey puts it, "In the degree in which the older group expresses itself politically we have the curious and indeed ironical condition that at just the time when measures of social readjustment are most needed, there is an increasing number of those whose habits of mind and action incline them to resist policies of social readjustment."

The deprivations and limitations of old age are by no means entirely biological. They are quite as much the result of the social order which we have developed. In a Society that has come to exalt economic success and to idealize youth, old age is regarded as a liability rather than a distinction. Traditions which developed with the frontier spirit when over one-half of the population was under 20 years of age still dominate national thought. The flagging powers of advancing years are stressed on every hand and as individuals approach middle life they are made ever mindful of the fact that their initiative, adaptability and creative ability are failing; they are no longer efficient; in short, that they are growing old. Soon they become aware that on every hand, opportunity is closed to them, that they must give away before the rising tide of youth. Then with the full realization that in the modern economic and social structure, there is no demand for their ripe experience, they yield to a sense of frustration and prepare to accept retirement as their lot.

This popular attitude concerning old age has been accepted by many professions and industries in which age limits have been placed upon employment, even though there is no scientific proof that hard work *per se* ever wears out healthy men and women. Inactivity leads to our undoing; activity keeps us alive. The worst shock that can come to any one is to be retired, particularly if that retirement is to make place for some one younger. Even those who are mentally alert and vigorous, when they are forced out of the activities of life in which they have so long played an important part, become old, often with incredible rapidity. Responsibility and duty serve as a stimulus to activity and interest. When they are removed, the urge to effort ceases and the characteristics of old age supervene. It is the exceptional individual who is able to function usefully in retirement. As a rule, the only people who profit from retirement are those who have developed interests aside from their business or profession and who have been able to plan and prepare systemat-

ically for their period of withdrawal from active work. Every physician of experience will subscribe to the statement of Roy Helton: "A sudden loss of sustaining habits and motives that have kept him in active competition for the rewards of labor, can within 6 months transform the busy lawyer, physician or merchant into an aged hypochrondriac." There is nothing so devastating to the self-respect and pride of any man as to find himself forced by retirement out of his active part in the affairs of life. To one who has enjoyed well-earned independence and walked with his head high among men, the abrupt assumption of a role of dependency, whether it be upon his family or the State, brings about a sense of uselessness and a retreat into the past.

The question of retirement from active employment is closely interwoven with the far-reaching economic and political aspects of the problem of aging. The falling birth rate in this country, the relative decrease in children under 5 years of age in the last three-fourths of a century, and the fact that the relative number of persons over 65 has almost doubled in this period have already been noted. In the meantime, the productive population aged 20 to 44, the age level of active employment, has remained constant. Obviously this is the group upon which falls the chief burden of caring for the young and the dependent older people. As child-labor legislation and more years devoted to education diminish the number of young workers, and enforced earlier retirement is diminishing the number of older workers, the group of productive workers grows smaller. Increasing responsibility falls upon them, because they must provide for the young, an actually increasing group of older people steadily being augmented by those who are retired, as well as the unemployed. Thus we find a minority group of producers subjected to the economic strain of caring for all the rest. In order to relieve individuals of this increasing burden, the government assumes, in part at least, this responsibility, but this "social security" can be provided only by increased taxation which in turn falls almost to a confiscatory degree upon the industries of the country which employ labor. Thus a vicious cycle creates a wholly unbalanced situation.

As a result of a discussion of old age pensions, one of the well-known columnists, Mark Sullivan, presents some startling figures of far-reaching implication. Under the caption, "Forty Million Workers Must Support 116,000,000 Others in 1965", he proceeds to state that, according to the conclusions of several experts, 25 years from now the total population

of the United States will be about 157,000,000 as compared to the present of about 133,000,000. Although this increase in total population is comparatively small, the important point is that the increase in the number of old people will be rapid and great. Those aged over 65 years will have increased from 46,000,000 to 60,000,000. Meanwhile, the number of productive workers aged between 20 and 65 will have remained about as now, around 80,000,000.

The first thing to notice, for its bearing on old age pension plans, is the doubling of the number of old folks. The second thing to notice is the material increase in the number of young folks. The third thing to notice is that the number at working age will remain about the same. For this last class, the prospect is disturbing; for they must support either privately or through taxation, the other two classes.

The working group must pay for the schools for the young and the pensions for the old and the combined number of old and young will have increased from 54,000,000 to 76,000,000, while the number of workers will not have increased, but will remain at about 80,000,000. Actually, the number of workers is not 80,000,000; about half of these are housewives or are otherwise not employed. Actually, about 40,000,000 workers will be supporting an equal number of their own age, about 60,000,000 young, plus 16,000,000 old, or a total of 116,000,000. In other words, two groups, the old and young, will be looking to the working group for support. Politically, the old will have two votes; the young will not.

The potentialities of such a situation, politically and economically are suggestive if not disconcerting. It has been suggested that one way to take political control from premature senility is to legislate the vote away from the old as we already do from the young. This would reduce the pressure block of the old to equality with the young. If the situation is allowed to exist undisturbed, consequences, in the judgment of experts, of an unpredictable and even revolutionary character may result. Speculations include a new kind of class war, a kind of political civil war between young and old; and another war, with young and old combined on one side and the workers on the other. Certainly there will be many consequences, having ramifications into every phase of life.

It is hard to visualize a more disastrous situation for any people than to allow their politics to come under the control of an idle old age group living without labor upon the bounty of the State or private enterprise.

As Helton has remarked with timely emphasis: "It will not be safe for America to permit the present psychology of old age to dominate even a powerful minority of our citizens." Four years ago we witnessed political campaigns based upon promises of financial assistance to the aged. For the most part they failed. Unless conditions are altered, similar efforts a decade from now may well meet with success, since the older group will have gained in numbers and political power.

What is the solution of the complicated problem presented by the steadily increasing group of the aging? They have been taught to believe that all they need is money. That alone is far from the answer to their difficulties. The inexorable laws of nature coupled with the trends of the social order we have built have brought to old age unhappiness and tragedy. This unhappiness is not entirely economic, it is primarily due to the inadequacies and maladjustments inherent in the old. That they often need money and are entitled to adequate support is axiomatic. The responsibility of Society to them goes further and involves a thorough and complete study, carried out with scientific detachment, of the needs of old age. Such a survey requires the intelligent coöperation of physicians, psychologists, psychiatrists and sociologists.

If we wish to alleviate the condition of the aged, the first step is to educate people to plan and to provide for their old age. Those who, through their own foresight, have established a certain degree of economic independence can approach the other aspects of growing old with more happiness and equanimity than the less fortunate. The pensions which have been contemplated or, as the result of legislation, are in effect, will doubtless mitigate to some extent the needs of the poor, but are wholly inadequate to maintain most older people at the social and economic level to which they have become accustomed. The aged have become or have been made acutely conscious of their incapacities and, as the result, have accepted the principle of retirement with little protest. Instead of expending their efforts in organizations designed to obtain for them a dole, it would be far more profitable for them and, at the same time, for the community, if they were aroused to the importance of combating in some effective manner, compulsory retirement. The greatest insurance for happiness at any age lies in work. There is no better outlet than to continue with the work which one has carried on throughout the greater portion of one's life. It is agreed that, because of their failing powers, it is inexpedient to demand of old people that they carry on

their maximal activities throughout life. It would seem possible, however, that in industries and professions an individual's work might be modified to meet his or her restrictions, thus permitting continued interest and active part in their accustomed occupations.

It is a fallacy to assume that older people no longer retain a capacity to learn; many seek opportunities for further study. Some extension of our educational system which would enable the older people who are mentally equipped, to seek diversion in further education would be desirable.

The aged in our midst must be impressed with the fact that, although Society is willing and eager to make every reasonable provision for their security and happiness, they must not acquire the attitude of accepting such succor passively but must put forth a constructive effort to help themselves. In the past, the mistake has been that older people have endeavored to compete with youth. Such an attempt must inevitably fail. They should be stimulated to develop interests and to occupy themselves within their capacities. They would profit by contacts and associations with those of their own age group. When we can offer those of older age opportunities for occupation and have imbued them with the idea of self-sustaining activities they will lose some of their willingness to sink into a parasitic existence.

In the foregoing, an effort has been made to show that the increasing number of older people in the nation presents a definite problem. A problem which if great today, will be far greater tomorrow. The issue is inescapable and must be met with frankness and fortitude. Its solution will require not only the best economic thought and political sagacity but also the sincere and whole-hearted coöperation of medicine and the biologic sciences.

HISTAMINASE: PHYSIOLOGIC EFFECTS ON MAN AND ITS THERAPEUTIC VALUE IN MEDICINE*

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HISTAMINASE is the name designated by Best and McHenry[1,2] for an enzyme-like substance which destroys histamine in the body of an animal. While Eustis[3] in 1915, working on the livers of turkey buzzards, first suggested that some enzyme might exist in the body which would inactivate histamine, it was not until 1930 that Best and McHenry isolated such a substance as a stable dry powder from beef kidneys. By means of perfusion experiments in animals, histaminase was found in relatively large amounts in the kidneys and large and small intestine and in moderate to small amounts in the other tissues of the body except the liver. However, in 1935, Steggerda, Essex and Mann,[4] using perfusion experiments in dogs, found that the amounts of histaminase in the liver were smaller than those in the kidneys but greater than those in other tissues they examined.

Although Best and McHenry had demonstrated the existence of histaminase in 1930, no apparent effort was made toward the clinical preparation or use of such a substance until some years later. In 1936 an intestinal mucosal extract which had properties said to be similar to those of the histaminase of Best and McHenry was introduced into this country from Germany. At that particular time we were especially interested in patients with hypersensitiveness to cold. If the liberation of histamine or a histamine-like substance, as had been suspected, was the causative agent in the pathogenesis of hypersensitiveness to cold, then this intestinal mucosal extract, histaminase, should be effective as a method of treatment in this condition. Therefore, the use of histaminase was begun in cases of hypersensitiveness to cold.

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While this work was being carried on in this country, reports of the use of histaminase in the treatment of various so-called allergic conditions began to appear in the same year in Germany.

Although we have studied the effects of histaminase in this country since 1936, it is only since its preparation in this country during the last nine months that adequate supplies of a well standardized preparation have been available for use in any large group of cases.* Both the physiologic and the clinical results are, therefore, preliminary in nature.

In order to determine in which clinical conditions the histaminase might be most useful and to attempt to evaluate the physiologic action of histaminase, it is necessary to review in part some of the work and some of the difficulties involved in the study of the physiologic reactions of histamine.

Since the isolation of histamine from ergot in 1910,[5] and from animal intestinal mucosa in 1911, by Barger and Dale,[6] the study of its effects on animals and man has formed the basis for many diversified investigations. The difficulty of isolating histamine quantitatively in crystalline[7,8] form from animal tissues and blood has been an obstacle in most of these studies. Many investigators have attempted to devise a suitable method for this purpose, but as yet, for the most part, the final analysis in the determination of histamine is still concerned with biologic assay.

Furthermore, inability to isolate histamine in its crystalline form has given rise to various names, such as H-substance, histamine-like substance and histamine-yielding substance, for those substances which produce histamine-like reactions physiologically. In most instances the parallelism between the responses of histamine and histamine-like substance is so apparent that, if one reviews the literature and observes the various responses, it is difficult to determine wherein they differ.

Histamine reactions in man may be divided into systemic and local skin reactions. The systemic reactions following the parenteral administration of histamine are characterized by a decrease in blood pressure, an increase in pulse rate simultaneous with marked flushing of the face, a rather intense headache and a subsequent rise in the gastric acidity.

In this paper it will be possible to mention only a few of the excellent investigations that have been made on the local skin reactions.

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* Histaminase was kindly supplied for this work by the Medical Research Department of the Winthrop Chemical Company as Histaminase and Torantil.

In 1913 Eppinger and Gutmann[9] in Germany noted the effects produced by intradermal injection of histamine and in 1912 Eustis[10] in this country stated the similarity of urticarial lesions to the reactions produced by intradermal application of histamine. He expressed the opinion that histamine is concerned with the production of urticaria.

The most comprehensive studies of the local skin reactions were made by Lewis and Grant[11] in 1924 and Lewis, Grant and Marvin[12] in 1927. They showed in cases of dermographia or urticaria factitia that the reactions to stroking of the skin in these subjects and the reactions from the intradermal injections of histamine in the same individuals were strikingly similar. Lewis has shown that the simultaneous production of wheals at various points on the skin of a subject with factitious urticaria may produce a flushing of the face similar in every respect to that obtained after the subcutaneous injection of histamine. They expressed the opinion that the liberation of histamine or of H-substance is probably the causative factor of the reactions. In these subjects, mechanical, electric, thermal and chemical stimulation produced the so-called triple response. They also observed that the increased permeability of the blood vessels of the skin was followed by a peculiar condition of partial or complete refractoriness to further stimulations of the same kind. As this condition of refractoriness became established, the increased permeability of the blood vessels of the skin disappeared. The development of a state of refractoriness by repeated, increasing doses of histamine in the intact animal had been demonstrated by Fühner[13] and Oehme[14] in 1912 and 1913. All these observations made possible a method of treatment later in clinical conditions.

The investigations concerned with the systemic effects of histamine are so varied and comprehensive that it would be impossible to include even a goodly number of them in this paper, but a consideration of one of the clinical phases seems logical at this point.

Urticaria attributable to cold was recognized as early as 1866 by Bourdon,[15] but it was not until 1872 that Blachez[16] gave the first classic description of this phenomenon. During the next fifty years various single reports were published on urticaria produced by exposure to cold, for the most part with only local manifestations, but in a few instances cases such as the one described by Duke[17] in 1924 were reported, in which urticarial eruption and a severe constitutional reaction occurred.

In 1927[18] and 1929[19] one of us (Horton) and Brown reported six

cases of hypersensitiveness to cold in which local and systemic reactions were so striking as to constitute a clinical entity. They were able to reproduce the local and systemic reactions by immersion of one hand in water at 8 to 10°C. for a period of six minutes. The local effects on the skin consisted of pallor during the period of exposure, followed by redness, swelling and increased local temperature on removal of the hand or exposed part from the cold water. After a latent period of from three to six minutes a characteristic systemic reaction developed, consisting of flushing of the face, a sharp fall in blood pressure, a rise in pulse rate, and in some instances a development of syncope.

When a tourniquet was applied to the arm for seven minutes while the hand was immersed in water at 10°C. and kept on for an additional eight minutes after the hand had been removed from the water, no local or general reaction occurred until the tourniquet was removed. This observation was important, for it ruled out the possibility of a reflex basis for the systemic reaction.

In addition they were able to reproduce the clinical syndrome by the subcutaneous administration of 0.5 mg. of histamine to the patient. They suggested that a physical agent such as cold might allow the release of a sufficient amount of this substance to produce both the urticarial response and the general systemic reaction. Because of the work previously mentioned on the development of a state of refractoriness from repeated, increasing doses of histamine, one of us (Horton) and Brown suggested that since the patient was sensitive to a chemical substance formed in the tissues, probably histamine, passive desensitization by repeated injections of histamine over long periods in minute doses, which were insufficient to produce a systemic effect, and gradual increase in the doses should prove an effective treatment and that probably the same should be true of repeated immersions of the hand in cold water. They were able to prevent both the systemic and the local reactions of various patients by means of immersion of one hand in water slightly above 10°C. for from one to two minutes twice a day for from three to four weeks or by means of subcutaneous injection of 0.1 mg. or less of histamine, twice daily for from two to three weeks. The treatment with histamine was confirmed by Bray[20] in 1932. In further work in 1932 one of us (Horton) and Brown,[21] by immersion in water at 10°C. of one hand of each of several patients who were hypersensitive to cold, produced a rise and fall of gastric acidity identical with that

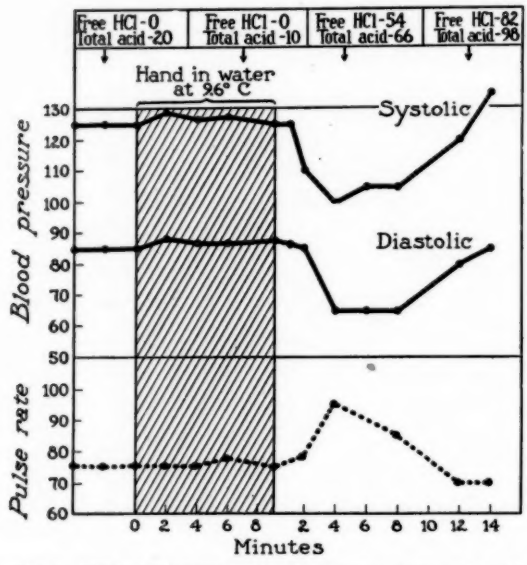

Fig. 1. Typical changes in blood pressure, pulse rate and gastric acidity in a case of hypersensitiveness to cold following immersion of one hand in water for nine minutes.

noted after parenteral administration of histamine (Fig. 1).

In 1936 the clinical and experimental investigation of twenty-two such cases was summarized.[22] These patients, eleven women and eleven men whose ages ranged from fifteen to fifty-nine years, exhibited abnormal local and systemic reactions following exposure to cold. Symptoms had been present for from one month to thirty years and consisted for the most part of urticarial wheals over the face, neck and hands and occasionally over the feet, thighs and trunk. Urticarial manifestations invariably followed exposure to cold wind, cold water or a cold environment. A number of the patients had swelling of the lips and one had dysphagia following ingestion of cold water or ice cream. Nine of the subjects had collapsed after swimming and four of them had to be rescued from the water. In sixteen of the twenty-two cases, the attacks were prevented by desensitization to cold or to histamine.

Histaminase has been given to ten patients with hypersensitiveness to cold. In all instances we reproduced the syndrome by immersion of one hand in water at 10°C. for seven minutes. Following administration

of histaminase for a number of days, the hand was again immersed in water at the same temperature and for the same period of time; at this time both the systemic and local reactions were slight or did not occur at all.

In some instances where the gastric acidity[23] was determined before and after administration of histaminase, the resulting figures showed a marked decrease in the rise of the gastric acids in the second test.

Because of this effect on gastric acidity, it was felt that further studies of gastric acidity should be made. Accordingly, studies were made with Gabrielsen[24] concerning the effect on the gastric acidity of five normal subjects when their whole body was immersed in water for fifteen minutes, the baths ranging in temperature, with intervals of 5°F. from 65° to 100°F. (18° to 38°C.). The gastric samples were obtained before the subject was immersed, at the end of fifteen minutes just before the subject was removed from the bath, and at fifteen and thirty minute periods after the subject was removed from the bath. While there was little or no rise in the concentration of the gastric acidity fifteen minutes after the immersion of the subject in water at body temperature or above, a rather definite rise in the concentration of gastric acidity occurred particularly fifteen minutes after the removal of the subject from water ranging from 65° to 85°F. (18° to 29°C.).

At a temperature of 75°F. (24°C.) there was no visible shivering and in an attempt to determine whether this rise in gastric acidity was due to an increase in metabolism, the basal metabolic rates were determined in one subject before and at the height of the rise. At those periods no change in basal metabolic rate was noted. At present we are carrying out further work in regard to this study. In order to determine whether this response of the gastric acidity of normal subjects fifteen minutes after immersion in water at 75°F. (24°C.) was a histamine or a histamine-like reaction, histaminase was tried. Commercially available histaminase is obtained from the intestinal mucosa and the kidney, and the oral preparation is enteric coated. Consequently it is probable that absorption only takes place after it reaches the intestine. Therefore, a special preparation was obtained which consisted of a fine white powder that could be suspended in physiologic saline solution and administered by means of the duodenal tube. We found in these five normal subjects that the introduction of histaminase into the duodenum by means of the duodenal tube thirty minutes before the subject was immersed in water

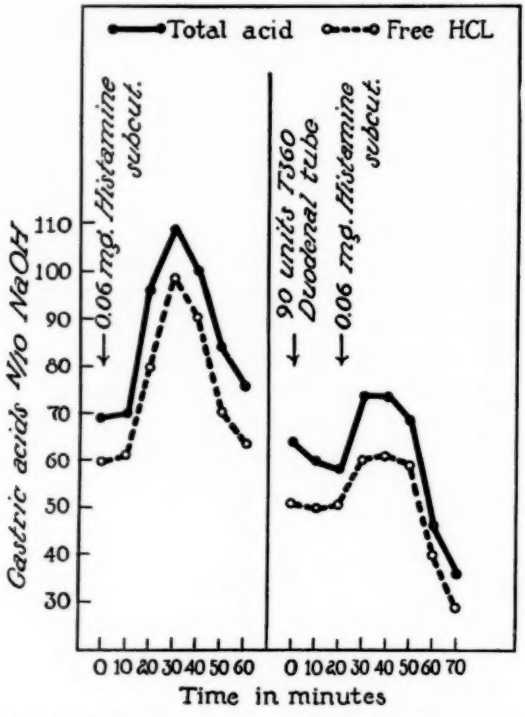

Fig. 2. Response of gastric acidity to subcutaneous injection of histamine. Response of gastric acidity after introduction into the duodenum of 90 units of histaminase (T360), preceding injection of the same amount of histamine thirty minutes later.

at 75°F. (24°C.) could inhibit the rise in gastric acidity produced by immersion of the subject in water at that temperature. Control studies were made with the introduction of physiologic saline solution into the duodenum.

Following these observations the normal response of the gastric acidity to subcutaneous injection of 0.06 mg. of histamine was determined. Several days after this response was accurately established, histaminase was introduced into the duodenum twenty-five to thirty minutes before subcutaneous injection of histamine. In this small series, following the introduction of the histaminase, the rise of gastric acidity was rather definitely decreased (Fig. 2).

In addition, again after the normal response to the subcutaneous injection of 0.06 mg. of histamine had been determined, a parenteral preparation of histaminase was injected intramuscularly thirty minutes before the usual subcutaneous injection of histamine. Again the rise in gastric acidity was decreased but was not completely inhibited except in two instances.

Furthermore, following the administration of histaminase by duodenal tube or intramuscular injection, the other systemic effects produced by administration of histamine, such as flushing of the face, decrease in blood pressure and increase in pulse rate, were practically abolished.

While the preparation, dosage and time may not have been optimal and the investigative work is incomplete and further studies are being carried out, these observations would seem to indicate that histaminase administered to man can inhibit the action of histamine or a histamine-like substance. The mechanism by which this is accomplished is unknown to us.

Since the use of histaminase seemed effective in the cases of hypersensitiveness to cold, in which we could produce the syndrome and note the results with considerable accuracy, further use of histaminase in other clinical conditions where histamine or a histamine-like substance might be a factor seemed feasible.

Headaches

Erythromelalgia of the head (histaminic cephalalgia) is a new clinical syndrome which was first described by one of us (Horton), MacLean and Craig[25] a year ago. It is characterized by unilateral headache which is sudden in its onset and excruciating in character and usually involves the neck, face, temple and eye. The distribution of pain does not follow that of any of the cranial nerves. There is almost invariably evidence of congestion about the involved eye and lacrimation is a prominent feature. Unilateral obstruction of the nose is frequently present during the attack. The patients have had none of the tic-like symptoms of trigeminal neuralgia and no trigger zones have been demonstrated. In contrast to the typical migraine headache, these patients do not have a hereditary incidence or an early history of migraine. There are no scotomatous or gastrointestinal accompaniments. These patients have found no relief from the usual methods of treatment.

These vasodilating headaches have been induced at will by the administration of histamine. Furthermore, treatment by "desensitization" with histamine has been previously carried out in a fairly large number of cases and has been previously reported. In view of the fact that we were able to induce these attacks at will by the subcutaneous administration of small amounts of histamine (0.1 to 1 mg.), it seemed logical to try out the use of histaminase in a group of these cases to see if good results could be obtained. Only a limited number of patients have been studied in this manner. However, in practically every instance where the patient has had the syndrome of "erythromelalgia of the head" these attacks have been eradicated by the use of histaminase. Not only do we feel that "desensitization" with histamine is a specific treatment for "erythromelalgia of the head," but our recent observations with the use of histaminase lead us to believe that it is almost as effective as "desensitization" with histamine. Further studies are being carried out.

Serum Sickness

Following our report on the effects of histaminase on patients with hypersensitiveness to cold, Foshay and Hagebusch[26] in 1939 reported the use of histaminase in the treatment of serum sickness. They found that the administration of histaminase, either orally or intramuscularly, brought marked relief to twenty of twenty-two unselected patients with serum sickness, most of them with the severe forms of the disorder. Eighteen patients were treated on either the first or the second day of illness, and sixteen obtained marked relief in from eighteen to thirty-six hours. Foshay and Hagebusch felt that the prophylactic use of the substance would prevent the occurrence of serum sickness in some instances and ameliorate the severity in others.

Cherry and Prickman[27] have reported an additional twenty-two patients who received histaminase in the prevention and treatment of serum sickness. The majority of their patients were treated for lacerations and compound fractures and were given routinely either tetanus antitoxin or the combined tetanus and gas gangrene antitoxin as a matter of prophylactic protection. Histaminase was administered to eight additional patients who received a variety of horse serums such as antistreptococcic serum, bacillary dysentery serum, and so forth. This group added to Cherry and Prickman's group made a total of thirty patients.

The effects of histaminase, generally from thirty to forty-five units

daily, were observed after well-developed serum sickness. Relief was observed in fourteen of seventeen cases in eighteen to thirty-six hours, and no relief was noted in three cases. When administration of histaminase and serum was started simultaneously because of positive patch skin tests or a history of allergy in thirteen cases, no serum sickness occurred in eight cases. In three cases a transient urticaria appeared which disappeared in twenty-four hours. In most instances this was due to the discontinuance of the drug on the seventh day which should have been continued through the tenth to twelfth day as the delayed serum sickness does not often occur until the seventh day. Since the urticaria was very mild, there was practically complete relief in eleven of these patients. No relief could be noted in two cases. While the series is small, it compares favorably with the results of Foshay.

Insulin Allergy

From the work of Lewis and his co-workers, histamine or a histamine-like substance was thought to be a contributing factor in a group of local skin reactions to subcutaneous injections of insulin and various horse serums. Hence, a study of the treatment of local skin reactions to injections of insulin was made by one of us (Roth) and Rynearson.[28] It had been noted that many patients experienced a mild local reaction to insulin when it was first administered. These mild reactions usually disappeared within one to two weeks.

However, this study deals only with cases of long duration in which there were very annoying skin reactions to insulin. At the site of each injection of insulin an area of from 2 to 6 inches (5 to 15 cm.) in diameter, which is red, raised, hard, tender and itchy, develops and may persist for several days.

The incidence of skin reactions among patients who are receiving insulin varies in different reported series. Collens, Lerner and Fialka[29] reported an incidence of 7.3 per cent, Allan and Scherer[30,31] of 15.1 per cent and Lawrence[32] of 30 per cent.

Many types of treatment have been tried for these local reactions to insulin, including change of the type of insulin, desensitization with very small amounts of insulin[33] injected intradermally and desensitization with small amounts of histamine. In one instance, Karr, Scull and Petty[34] sensitized a rabbit to the patient's serum and then gave the patient the active serum of the rabbit. The allergic reactions disappeared.

Forty-five to sixty units of histaminase were administered orally each day to each of twelve patients with this type of local insulin allergy. In ten cases daily injections of insulin could be given without local skin reactions in from two to ten days after the administration of histaminase was begun.

Local Skin Reactions to Subcutaneous Injections of Antistreptococcic Serum

Another group of thirty cases in which similar annoying local skin reactions persistently developed after injections of antistreptococcic horse serum was studied. The reactions consisted of areas of from 2 to 5 inches (5 to 13 cm.) in diameter at the site of injection which were red, raised, hard, tender and itchy. These areas generally persisted for four to five days. Histaminase was administered orally to these thirty patients after definite soreness and itching were developed. A history of allergic manifestations was obtained in nine cases and, when positive skin patch tests with the various antistreptococcic horse serums were made, positive skin reactions to these patch tests were obtained in twenty-seven of the thirty cases. In the other three, soreness and itching at the site of injection were noted only after the concentration of the injected serum had been increased. In thirteen of the cases local reactions were prevented in two to four days by 45 to 60 units of histaminase administered orally, and the patients were able to finish their course of serum treatment. In six cases there was some improvement but not a more rapid disappearance of the local reaction. In eleven of the thirty cases the serum treatment was stopped because of the persistence of the local reaction following each injection. Again this is not a large series and although these results are encouraging, a considerably larger group of cases should be studied.

Urticaria

It has been thought by certain investigators that urticaria may be in some way related to release of histamine or histamine-like substances and on this theoretic basis the use of histaminase seemed logical in cases of urticaria.

In 1939 Laymon and Cumming[35] reported the use of histaminase in seventeen cases of urticaria. They noted a clinical cure in 59 per cent of their patients; 12 per cent were improved and 29 per cent were un-

improved. Because of the small number of patients treated with histaminase and the relatively long duration of the condition, they did not draw any definite conclusions concerning the value of histaminase in the treatment of urticaria.

Forman[36] in a study of ten cases of chronic urticaria demonstrated that histaminase was helpful in the treatment of chronic urticaria except for one case in which more severe hives with nausea and heartburn was produced by the administration of the capsules. It was found that the patient gave skin reactions to cow's milk and beef.

Histaminase was administered to fourteen patients who had urticaria. Where the attacks occurred spontaneously in spite of the elimination of many foods and the presence of no known precipitating factor, almost immediate cessation of development of urticarial lesions was obtained in fourteen to twenty-eight hours. With continued treatment, this relief lasted a period of three weeks while the patients were under observation. One patient has obtained only partial relief. Two patients in whom urticaria developed during pregnancy, remained free from urticaria when 30 units a day were given. When the dose was less than that amount, urticaria reappeared. In five of six cases various drugs, such as liver extract, cobra venom, treparsol and morphine, precipitated attacks. Complete cessation of the development of urticarial lesions was obtained in twelve to forty-eight hours and the lesions did not reappear with the continuance of the various drugs. One patient who had a fourteen year history of asthma obtained only a partial cessation at the end of forty-eight hours. Another patient with giant urticaria of one year's duration was not relieved.

While these effects are interesting and encouraging, we realize that there are a number of types of urticaria and our series is too small to justify any conclusions as to the effects of histaminase in a condition which is characterized by great irregularity in the appearance of the lesions and their spontaneous disappearance.

Vasomotor Rhinitis

Because certain cases of vasomotor rhinitis are allergic in nature, Prickman, Lillie, Fleming and one of us (Roth)[37] made a study of forty patients with vasomotor rhinitis.

In 1937, Adelsberger[38] reported very favorable results in the treatment with histaminase of eight patients with allergic rhinitis. He stated

that five of these patients were cured, one was improved and two received no benefit.

In our study the nasal membranes were observed before and after histaminase was administered orally. Thirty to 50 units were given three times a day before meals to each of the patients for seven to fourteen days. Eighteen patients were relieved of the nasal obstruction, watery discharge and sneezing; a definite improvement in the appearance of the nasal membranes could be seen. The condition of eight patients was improved but not to the extent experienced by the eighteen previously mentioned. The remaining fourteen patients did not receive appreciable relief. It is interesting that, following the intravenous administration of histamine to patients, numerous attacks of vasomotor rhinitis have been produced.

Summary

We have presented our physiologic evidence on the relation of histaminase and histamine in man. These observations are limited in number, and the work is far from complete. The development of such studies has been slow and impeded by the lack of a readily available method for quantitative isolation of crystalline histamine from blood and tissues.

We have observed 150 patients with various clinical conditions to whom histaminase has been administered orally. No untoward effects with doses as high as 125 units in a day were noted in any of these patients.

There is evidence to show that histamine or a histamine-like substance is a factor in the pathogenesis of certain clinical disorders characterized by local or general hypersensitiveness and in these clinical disorders histaminase has been used in an effort to inhibit the action of these substances.

From the results of this preliminary report and on the basis of our experience and that of others, histaminase seems to be an effective therapeutic agent in certain cases of clinical hypersensitiveness.

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THE MEDICAL MANAGEMENT OF DISORDERS OF THE BILIARY TRACT*

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IT IS impossible to cover the whole field of management of biliary tract disease in a short period of time, therefore, I shall discuss principally some developments of recent years which have altered materially concepts previously held in regard to diagnosis and treatment. This subject is of great importance because the biliary tract is usually considered to be the most common cause of digestive symptoms (Rehfuss,[1] Mentzer[2]). There are moreover, great differences of opinion as to certain facts: the relative importance of various factors causing biliary tract disease; the types of cases responding best to medical or surgical therapy; the value of various methods of medical treatment. It is to problems of this character that my time will be mainly devoted.

GENERAL CONSIDERATIONS

Extra-Hepatic Physiology: Since an understanding of biliary tract disorders is necessarily based upon a knowledge of normal function, a brief review of biliary tract physiology is justified. The most essential fact, and the one most commonly overlooked, is that the biliary tract as well as the rest of the digestive system is under the direct control of the autonomic nervous system.[3,4] With remarkable consistency, the liver continuously secretes the bile which during fasting is prevented from entering the duodenum by the common duct sphincter of Oddi (Ivy[5]). The dilute hepatic bile is therefore diverted into the gall bladder, which acts not only as a reservoir and equalizer of biliary tract pressure, but also concentrates the bile four to ten times, mainly by the absorption of water (Ravdin[6]). According to most investigators, the concentrated bile is discharged into the duodenum by the more or less simultaneous contraction of the gall bladder and the relaxation of the common duct sphincter (Lyon[7]). This action is instigated by the hormone cholecys-

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tokinen, which is formed in the duodenum as the result of stimulation of food chyme (Ivy[5]). Following the discharge of concentrated bile in response to food, the common duct sphincter again closes and the contracted gall bladder is once more filled with bile.

A study of pressure relations in the biliary tract affords a means of understanding the cause of certain symptoms and functional disturbances. The common duct sphincter is capable of resisting a pressure of 75 cm. of water, whereas the gall bladder is capable of exerting a pressure of only 30 cm. (Ivy[5]). The ways in which normal physiological action may be disturbed by functional disorders, infection, and obstruction will be discussed later.

Factors In Diagnosis

The History: The diagnosis of biliary tract disease depends primarily upon an accurate history, which must include in addition to an account of digestive symptoms, a study of the individual, his personality and environment. It is only by this approach that functional disturbances ultimately may be determined; by the relationship of acute symptoms to emotional disturbances, business or financial worries, unhappy marital relations, or conditions leading to physical or nervous exhaustion. Further inquiry will in many cases reveal a relationship between symptoms which apparently originate in the biliary tract and that large group of disorders of gastric, duodenal, and colonic physiology.[8] That the endocrine system is also indirectly involved in the production of these symptoms is suggested by their frequent onset during or following the menopause, as well as their being associated with disorders involving the thyroid gland.

Pain: The accuracy of the history and diagnostic tests is best shown by a study of the findings in patients coming to operation. In a series of 250 cases carefully reviewed, we have arrived at several conclusions of interest. The first is the fact that biliary colic, regardless of how typical the attack may be, does not necessarily mean stones. This knowledge deserves emphasis because frequently colic is considered proof of stones and therefore an indication for operation. Most recent evidence seems to indicate that colic results from the sudden overdistention of either the gall bladder or the common duct as the result of obstruction to the outflow of bile. The cause of the obstruction may be stones, spasm or organic disease (Morley,[9] Hurst,[10] Zollinger[11]).

Because pain proved to be the most prevalent symptom in the series studied, further observations of its characteristics seemed justified. While biliary tract pain is described as typically originating in the right upper quadrant, no less than half of these patients described the pain as being in the epigastrium. Hurst,[10] incidentally, has made similar observations. Radiation furthermore was in many cases atypical, being to the left side or precordium, especially with obstruction of the cystic or common ducts (Carter[12]). Among other symptoms of particular significance were nausea and vomiting, which occurred most commonly with overdistention of the common duct, as noted by Zollinger.[13] Chills and fever or jaundice were usually associated with both obstruction of the common duct and infectious cholangitis.

The Cholecystogram: The routine oral use of the double dose of dye has been attended by a notable increase in accuracy, particularly in the detection of stones (Stewart and Illick[14]). Technique has furthermore been improved by the use of paregoric to intensify the gall bladder shadow through its effect on the sphincter of Oddi, as well as to prevent loss of dye by diarrhea. The removal of excessive gas by enemas and the hypodermic injection of Prostigmine have also proved useful procedures.

In the interpretation of cholecystographic findings, a correlation with operative findings by Heyd, Carter and Hotz[15] has shown that the intensity of the gall bladder shadow is, in most cases, a reliable indicator of its concentrating ability, provided functional disturbances have been ruled out. In other words, faint visualization of the gall bladder which filled and emptied normally indicated active or past infection with fibrosis in 87 per cent of the patients coming to operation. Stones are difficult to visualize in these cases. However, a poor concentration of dye and consequently a faint visualization was found to occur with a gall bladder capable of normal concentration, when there was a disturbance of liver secretion or interference with the flow of bile into the gall bladder. On the other hand, a normal visualization of the gall bladder may occur in the presence of definite disease, particularly if there is impaired emptying. Further observations have shown that a lack of gall bladder shadow is not a reliable diagnostic sign unless the dye can be simultaneously visualized in the colon. This is assurance that the dye has been taken and has not been lost by vomiting or diarrhea. The most common operative finding in patients having had pain and showing no visualization of the gall bladder is a cholesterol stone impacted in the

cystic duct. Statistical studies have almost invariably shown that the stones found at operation can actually be demonstrated in the cholecystogram in only about 25 per cent of patients.

The cholecystogram, furthermore, affords usually unrecognized evidence of functional disorders in the enlarged gall bladder shadow, which is frequently of unusual intensity; confirmatory evidence is found in a delay in emptying of the gall bladder following a fatty meal. The general use of cholangiography (Mirizzi[16]), or visualization of the biliary tree by the injection of a radiopaque substance through the "T" tube during or following operation, should greatly reduce the incidence of postoperative colic due to retained common duct stones. Our conclusions in regard to the x-ray studies are that although these methods have attained a remarkable degree of accuracy, they must not be considered entirely infallible. They are simply a part of our diagnostic investigations; all other findings must also be taken into consideration in arriving at a final diagnosis.

Biliary Tract Drainage: Under the circumstances, it is indeed fortunate that there is available a dependable supplementary diagnostic method; that of biliary tract drainage (Lyon[7]). Numerous investigators have proved that the microscopic examination of the biliary sediment affords reliable evidence of infection or stones, just as similar evidence may be found in an examination of urinary sediment (Lyon[7], Piersol and Bockus,[17] Rehfuss,[1] Rousselot[18]). Investigation of several hundred patients coming to operation, however, shows that crystalline sediment may indicate stasis rather than stones.

Furthermore, it is now possible to demonstrate with considerable accuracy actual infection of the biliary tract with the encapsulated duodenal tube.[19] In a series of 120 operative patients reported by Twiss, Carter and Hotz,[20] preoperative duodenal drainage showed all specimens of duodenal bile to be sterile in seventy-four of seventy-five cases where the biliary tract was proved to be sterile by specimens obtained at operation. Of twenty-eight cases showing positive duodenal cultures of significant organisms, twenty-five had identical types of organisms in the biliary tract at operation. The encapsulated tube and its use have been described by Twiss and Phillips.[21] These facts are of great practical importance because in all published reports the least satisfactory results of cholecystectomy have been obtained in those patients having neither stones nor infection.

Aside from its value in the demonstration of organic pathology, biliary tract and common duct drainage has furnished much of the evidence upon which the vast and growing volume of literature pertaining to functional disorders of the biliary tract is based. Its contributions here are mainly the demonstration of abnormalities in gastric acidity, which are found in the majority of patients with biliary tract disease, and the variations in the amount and concentration of bile obtained following stimulation. There is, moreover, no test of greater accuracy for complete obstruction of the common duct, a finding usually indicating malignancy, or for the absence of pancreatic ferments, which is sometimes found in pancreatic disease. A word of warning must here again be sounded, however, for no conclusion can be based upon the findings of a biliary tract drainage which has not been properly performed.

A discussion of diagnosis cannot of course be left without mentioning that there is a multitude of tests which have been devised for the purpose of demonstrating impairment in liver function or differentiating between the obstructive and intrahepatic types of jaundice. Each of these has its enthusiastic adherents, few, however, have come into general use or obtained unanimous approval. While many of these procedures have undoubtedly great value, a discussion of their relative merits would be far beyond the scope of the present paper.

Differential Diagnosis: Failure in treatment may indicate that the symptoms for which the patient is being treated did not originate in the biliary tract, or that the relationship between the biliary tract symptoms and other disorders was not sufficiently well understood. Among other disturbances which we consider to be due to an imbalance of the autonomic nervous system is spastic colitis, characterized usually by abdominal pain, constipation, mucus in the stool, a spastic colon and the finding of hyperactive reflexes.[22] Among other apparently related conditions are pylorospasm and duodenitis, which are usually characterized by some relationship of symptoms to the intake of food. Another condition is peptic ulcer, the diagnosis of which is suggested by pain occurring regularly before or after meals, or at the same time every night. Inflammatory lesions of the appendix and urinary tract quite commonly produce difficult diagnostic problems; the presence of a right-sided ureteral stricture or renal calculus may also be confusing. The finding of gall bladder dysfunction secondary to such conditions should not prevent attention

being focused primarily upon the original cause of the patient's symptoms. In any patient having precordial or epigastric pain, we must carefully determine whether the pain originates in the biliary tract or in the heart, remembering that both may be involved. Finally, the possibility of tabetic crises must never be forgotten.

Some Problems In Management

In discussing the medical management of biliary tract disease, the question which immediately becomes apparent is, "What type of case do you include in this group?" The answer is that every patient with biliary tract disease is a candidate for a careful complete diagnostic investigation, followed by continued medical supervision, regardless of the necessity of surgical intervention. Both infections and functional disorders of the biliary tract are with few exceptions chronic and recurrent in character, as careful follow-up investigations have shown. The situation has been admirably summarized by Lahey and Jordan:[23] "The management of biliary tract disease, like the management of almost all other intraäbdominal diseases, has become a joint problem of the surgeon and internist. While the treatment of gall bladder infection and stones and of cholangitis are admittedly surgical, the diagnosis and postoperative treatment of these conditions present problems of great interest to the internist."

The initial and immediate problem which confronts the physician in any given patient might be expressed by the questions:

"Is this a medical or surgical case?"

"What are the indications for treatment?"

Satisfactory answers to these questions are furnished by an adequate diagnostic work-up, which quite frequently necessitates more information than can be obtained by the usual history, physical examination, and cholecystogram. Not even direct positive evidence of the fundamental factor of infection can be obtained by these limited means. However, the necessary information may be obtained by other methods such as biliary tract drainage, chemical examination of the blood, and liver function tests.

The first step in diagnosis is a differentiation between organic disease and functional disorders of the biliary tract. Although control of the entire digestive tract by the autonomic nervous system has always been known, the mechanism of the biliary tract has only recently been suffi-

ciently understood to be of practical value. A study of functional disorders of the biliary tract was probably originated by Westphal,[24] the importance of whose concepts has been stressed in the American literature by Ivy and Sandblom,[25] under the term of biliary tract dyskinesia. The basic classification of these disorders is into atonic and hypertonic types of gall bladder enlargement.[26,27]

Functional Disorders: The atonic type of gall bladder enlargement is commonly found in patients showing a general debility, usually in those of middle age or advanced years who are addicted to sedentary habits and overeating. Their history is characterized by dull pain or discomfort, especially after meals, belching, distention, nausea, and constipation. The cholecystogram shows an enlarged balloon-shaped gall bladder with impaired power of evacuation, as demonstrated by lack of emptying following the fatty meal. On biliary tract drainage, there is usually a deficiency of free hydrochloric acid, with a large amount of concentrated bile which is obtained only after stimulation of the gall bladder with olive oil.

The hypertonic gall bladder associated with gastric hyperacidity often gives, in addition to the dyspepsia previously described, symptoms of colic and heartburn. On physical examination there may be tenderness in the right upper quadrant. This, however, seems to be due to overdistention of the gall bladder and disappears following duodenal drainage. The cholecystogram shows in these cases a tubular type of gall bladder enlargement with a dense shadow, commonly with a delay in emptying following the fatty meal. Biliary tract drainage findings include gastric hyperacidity; concentrated bile is obtained following stimulation. Cultures of duodenal bile are usually sterile.

The hypertonic gall bladder of the reflex type is similar in symptomatology to that described with gastric hyperacidity. Acute symptoms are more apt to follow an emotional disturbance or physical or nervous exhaustion. Here again there may be tenderness in the right upper quadrant, which disappears after duodenal drainage. The cholecystogram differs in showing, during periods of freedom from pain, prompt and almost complete emptying following the fatty meal. On biliary tract drainage concentrated gall bladder bile is easily obtained following stimulation with magnesium sulphate. Cultures of duodenal bile are again sterile. The essential feature of the hypertonic reflex gall bladder, however, is the presence of some source of reflex irritation which results in

a spasm of the common duct sphincter and a resultant overdistention of the gall bladder and common duct. The reflex cause may be in the central nervous system, induced by worry or fatigue, or it may lie in some pathological condition of the abdominal cavity, such as a chronic appendicitis, renal calculus or pyelitis. Carter and Hotz[28] recently reported three cases in which improved function of the gall bladder followed the removal of a diseased appendix.

In functional disturbances particularly of the hypertonic type there are, practically invariably, evidences of disturbed function of the autonomic nervous system, which controls the function of the entire biliary and digestive tracts. It is therefore of clinical significance to be able to ascertain the presence of an imbalance of the autonomic nervous system. While patients having this disorder may be the picture of composure, they are usually of the nervous, hyperactive, worrying type. Environmental disturbances which cause symptoms can frequently be found by a careful history. The most common physical findings are a postcervical tension and tenderness, dilated pupils, a spastic colon (with a palpable tender sigmoid and a dilated cecum), and generally hyperactive reflexes.

Chronic Non-Calculous Cholecystitis: Since this term is in use to designate cases of every possible degree of inflammation and infection,[29] as well as many in whom there is no infection whatsoever, it is first necessary to define our terms. Graham[30] and Mackey[31] have suggested the following classification: (1) Minimal lesion, wall of gall bladder slightly thickened, few lymphocytes in wall, concentrated bile in the gall bladder, (2) cholesterosis, (3) chronic catarrhal cholecystitis—edema of mucosa, greater lymphocytic infiltration, some muscular thickening, (4) chronic fibrous cholecystitis, markedly thickened walls, diverticular crypts, an absence of cuboidal epithelium, usually associated with calculi. Heyd, Carter and Hotz[15] offer a similar but somewhat more comprehensive classification, in which dysfunction is considered a preliminary step to stone formation and infection, as well as the various subsequent pathologic changes in the biliary tract. In non-calculous cholecystitis, an accurate initial classification is essential, because the effectiveness of cholecystectomy in the relief of symptoms is directly proportional to the amount of pathology present. A statistical study of operative cases and pathological specimens has shown in most instances that where symptoms have not been relieved by cholecystectomy there is little or no pathological change in the gall bladder wall.

The presence of chronic cholecystitis may be suspected with a history which includes pain of the character previously described, dyspepsia, an intolerance for fats, and constipation. Symptoms of more extensive pathological changes are nausea, vomiting, chills, fever, jaundice, and loss of weight. Tenderness and spasm of the right upper quadrant are to be found during active phases of the disease. As indicated by a study of those patients coming to operation, the cholecystogram will in most cases show impairment in the degree of visualization of the gall bladder; with no visualization there are generally stones. The biliary tract drainage usually shows pathologic elements in the biliary sediment, an impaired response to stimulation in obtaining concentrated gall bladder bile, and positive cultures in specimens of duodenal bile obtained under sterile precautions.[32] An additional finding, common during active stages of infection, is a moderate elevation of the icterus index reading,[33] even in the absence of jaundice.

Since differentiation between true cholecystitis and dyskinesia is highly important, the differential factors as demonstrated primarily by operative findings should warrant a brief discussion. The symptoms apparently most suggestive of cholecystitis are acute prolonged attacks of pain, chills, fever, loss of weight, and jaundice. Pain is usually associated with soreness or tenderness in the right upper quadrant. In cholecystographic studies, cholecystitis cases usually show faint or no visualization of the gall bladder. On the other hand, the cholecystogram in uncomplicated functional disorders shows a strong concentration of dye and a characteristic enlargement of the gall bladder with delayed emptying after the fatty meal. The fact must be constantly kept in mind, however, that in many patients both functional disorders and infection are present.

Having arrived at the diagnosis of chronic cholecystitis, it is next necessary to determine whether medical or surgical treatment is preferable. Surgery is usually necessary with a history of recurrent acute attacks of pain, nausea, vomiting, chills, fever, or jaundice. Patients with these symptoms rarely respond well to medical treatment. In a study of 3872 operative cases reported by Heyd, Carter and Hotz[15] these symptoms have been found to be associated most frequently with advanced pathology involving the common duct. The advisability of surgery is confirmed if the history described is associated with findings of acute tenderness, spasm, or a mass in the right upper quadrant; faint or no

visualization of the gall bladder; biliary drainage findings of an absence of normally concentrated gall bladder bile. Further evidence is furnished by the presence of pathologic microscopic elements and positive cultures of pathogenic organisms in the duodenal bile. With these findings there may be a moderate elevation in the icterus index reading. Medical treatment is indicated (in the absence of the recurrent acute symptoms previously mentioned) when the cholecystogram and biliary tract drainage indicate a fairly normally-concentrating gall bladder, with sterile or positive cultures of duodenal bile, and a relatively normal icterus index. Mentzer[34] however states, "all patients with chronic non-calculous cholecystitis are entitled to a trial period of medical treatment."

Cholesterosis: By cholesterosis of the gall bladder is meant the "strawberry gall bladder" described by Moynihan and MacCarty.[35] The title is derived from the appearance of the mucous membrane of the gall bladder, which is covered with tiny yellow plaques of cholesterol esters and fats. While the causes of this condition and the best methods of treatment have aroused a great deal of speculation, a very comprehensive study by Mackey[31] seems to indicate that the deposits in the wall of the gall bladder are simply the result of excessive absorption of cholesterol from a supersaturated solution of gall bladder bile. The conclusions of this author are that cholesterosis of the gall bladder is in itself not entitled to the designation of a clinical entity; that it cannot be diagnosed with assurance clinically; and that the symptoms and indications for treatment in this condition are entirely dependent upon the degree of concomitant cholecystitis.

Cholelithiasis: While in general cholelithiasis is conceded to be surgical, the problem of the patient with stones and without acute symptoms will always be with us. An excellent study of stone formation has been reported by Sweet.[36] In these cases the gall bladder may visualize and empty normally or there may be no visualization in the cholecystogram and no concentrated bile obtained on duodenal drainage. Additional findings may be positive bacteriological cultures of duodenal bile and a moderate elevation of the icterus index. In the latter group is usually found active infection[37] or a non-functioning gall bladder with a calculous obstruction of the cystic duct. There is at other times advanced pathology of the gall bladder, common duct and liver (Heyd, Carter and Hotz;[15] Heyd and Killian;[38] Graham[30]). Recurrent acute attacks and laboratory findings of infection, advanced pathology, or a non-

functioning gall bladder would seem to justify advising prompt surgical interference, since impairment in the blood supply in many cases results in gangrene or perforation of the gall bladder. In 167 cases of cholelithiasis, under observation but not operated upon for various reasons, 10 per cent developed acute cholecystitis.

Acute Cholecystitis: The first and foremost consideration, and this is a fact which is frequently overlooked, is that acute cholecystitis is in approximately 90 per cent of the cases an acute exacerbation of a chronic cholecystitis, with cholelithiasis. Therefore, advanced pathology may be suspected in the patient with acute symptoms, especially if there is a prolonged history of indigestion and presence of acute tenderness and a mass in the right upper quadrant. Especially in the aged, the absence of fever and leukocytosis is by no means uncommon, even in the most advanced stages of pathology. The sedimentation rate may serve as a more reliable indication of the severity of the infection, or of the presence of empyema or gangrene of the gall bladder.

These facts have a very definite bearing on the spirited and prolonged controversy over the relative merits of the "immediate" and "delayed" operation in acute cholecystitis. Statistical studies have proven both sides to have been at least partially right in their contentions. Heuer states that gangrene and perforation occur in at least 20 per cent of all cases of acute cholecystitis not operated upon promptly. Hotz[39] in a study of 574 cases of acute cholecystitis, states that gangrene was found at operation in 17 per cent of the cases and perforation in 16 per cent. The general mortality in this series was 10 per cent; in acute perforated cholecystitis the mortality was 26 per cent. With peritonitis, which occurred in 77 per cent of patients with perforation, the mortality was 39 per cent. Hotz[40] concludes that "perforation of the gall bladder during an acute attack is as frequent and as fatal from a statistical review as that in acute appendicitis."

In regard to the optimum time for operation in acute cholecystitis, the picture has been in the past confused by statistical studies based upon the time of operation after the patient has entered the hospital. By a study of the elapsed time from the onset of acute symptoms, Hotz[39] found that the mortality showed a great variation, which depended upon the day of illness upon which the operation was done. From the first to the fourth day there was a progressive decrease in mortality from 12 per cent to 4 per cent; after the fourth day there was a progressive rise. The

conclusions based upon these studies were that prompt operation in most cases of acute cholecystitis is preferable, provided a period of at least 24 hours is allowed in the hospital to prepare the patient for operation. The essential features of preparation consist in relieving dehydration and building up the glycogen reserve of the liver, by giving dextrose by mouth and infusions if necessary.

Therapeutic Considerations

The principles of treatment here outlined have been formulated and followed during the past ten years in the Biliary Tract Clinic of the New York Post-Graduate Hospital. A detailed diagnostic investigation has been completed in 2,100 patients; conclusions as to the results of treatment are based upon approximately 20,000 clinic visits. The diagnostic routine has included the cholecystogram, biliary tract drainage, and chemical analysis of the blood. Practically all patients suspected of having infection or coming to operation have had cultures made of bile; for several years this has been obtained by means of the encapsulated duodenal tube.

Preoperative Care: Surgical patients are admitted when possible several days before operation. During this period the patient is given a high caloric, high carbohydrate diet, low in proteins and fats. Lumps of sugar, dextrose or candy are given every two hours; water or fruit juices every hour or two. When necessary, dehydration is relieved by clyses or intravenous infusions of 5 per cent glucose, care being taken not to overload the circulation. With jaundice, which involves the possibility of hemorrhage and results in a greatly increased mortality, the preoperative administration of bile salts and vitamin K is indicated for at least 4 days preceding operation. The amounts are judged by the results of the prothrombin time (Snell, Butt and Osterberg[41]).

Postoperative Care: In several hundred patients reporting for relief of digestive symptoms following cholecystectomy, practically none was following any dietary restriction. Most patients had been told that they were "cured" and could "eat anything." In our experience, recurrent symptoms are less common with a diet restricted in the intake of fats and foods high in cholesterol,[42] as well as those foods which are indigestible and high in roughage. We also feel that the general hygienic care of the patient merits continued supervision, especially in regard to the intake of an adequate amount of fluids, sufficient exercise, and the avoidance of

overeating and constipation. Medication in these patients is seldom needed and is given only in accordance with specific indications furnished by the history, physical examination, or laboratory findings.

Medical Regime: The general principles of treatment in medical patients are based upon the initial diagnosis and the results of diagnostic tests, as well as upon the personality of the patient and his environment. An effort is made to direct treatment to physiological needs, whenever this is possible. In functional disorders, rest or a complete change of environment is frequently beneficial, as is the removal or treatment of any pathological conditions of the abdominal cavity. General hygienic care is of the utmost importance in all ambulatory patients, especially in those having infections. Removal or treatment of focal infections should also receive consideration. The more serious conditions, particularly those associated with jaundice and fever, should have bed rest.

Diet: The opinion of Chauffard and Rehfuss and Nelson[1] has been confirmed by our experience, in that there is no more important element than diet in the treatment of disorders of the gall bladder or liver. Diets formulated in our clinic for gall bladder disease are of three types:[43] (1) Low fat and low cholesterol, (2) Modified Sippy, (3) "Stimulating," or relatively high cholesterol and fat. The diets and the indications for their use have been described in detail by Carter, Greene and Twiss.[12]

The low cholesterol and low fat types of diet have been in use for many years. The foods highest in cholesterol are egg yolk, brain, liver, kidneys, and sweetbreads. Both fats and cholesterol cause contraction of the gall bladder and when taken in excessive amounts tend toward a hypercholesteremia. The indications for the use of these diets are hypercholesteremia, cholelithiasis, a history of intolerance for fats, and any condition which interferes with the contraction of the gall bladder, such as inflammation or obstruction of the cystic or common bile ducts. The use of a low cholesterol and low fat diet results in a lowered blood cholesterol in most cases. Since weight variations in gall bladder disease are frequently extreme, this group of diets consists of the No. 1 diet, which is low in calories, and the No. 2 diet, which is high in caloric value, chiefly through intermediate feedings and the addition of foods high in carbohydrates.

The modified Sippy diets with intermediate feedings are intended for the patients with gall bladder disorders with gastric hyperacidity and the so-called hypertonic, hyperacidity type of gall bladder enlargement.

Clinically about 25 per cent of chronic disorders were found to fall in this group. This type of diet is also indicated in duodenitis, pylorospasm and in extreme degrees of spastic colitis. The 3 A diet is a strict carbohydrate diet with intermediate feedings, the 3 B diet a maintenance diet with the addition of meat.

By "stimulating" types of diet is meant those designed to relieve biliary stasis and to promote evacuation of the flaccid or atonic type of gall bladder. The contraindications to their use are fat intolerance, hypercholesteremia, cholelithiasis, active infection of the gall bladder and obstruction of the cystic or common ducts. Our diet No. 4 is low in caloric value; diet No. 5 is high in caloric value.

Another very important member of the dietary group is diet No. 6, which is high in carbohydrates and calories, low in proteins and fats. This diet is used in jaundice of all types, acute liver damage, and cirrhosis of the liver. The great value of this type of diet in relieving the ascites of cirrhosis has been demonstrated by the staff of the Mayo Clinic. It is also useful in building up the glycogen reserve of the liver before operation, and in increasing the weight of the patient who is suffering from malnutrition or recent weight loss.

Medication: Aside from the dietary and hygienic measures discussed, efforts are made to give medicines only in accordance with definite indications. Among the relatively few which we have been using are the following:

Laxatives: Constipation is one of the most common symptoms associated with biliary tract disease. As a result, the liver probably frequently suffers from impaired function due to actual infection or toxic absorption as suggested by Rehfuss[1] and by Bassler.[44] Where possible, an adequate amount of exercise and fluids are advised. Saline laxatives have a definite place; among those most effective are Epsom salts, Carlsbad salts, sodium phosphate, sodium sulphate and many similar preparations. In spastic hypertonic conditions, lubricants are preferable, such as mineral oil, agar, Irish moss, and combinations of these medicines. Bile salts and their combinations with various types of cathartics should be limited to patients who do not have spastic colons or biliary dyskinesia. Cathartics in general are contraindicated except in the aged, in whom vitamin B is especially useful.

Alkalies: The prevalence of gastric hyperacidity with disorders of the gall bladder is rarely suspected, because the gastric acidity of these

patients is hardly ever tested. However, in many with colic, heartburn and indigestion almost immediate relief can be obtained by the modified Sippy diet and alkalies following meals. These medicines give best results when taken an hour after eating. Among medicines which have proved satisfactory are equal parts of calcined magnesia and calcium carbonate, to which an equal part of bismuth subcarbonate may be added if desired. By adjusting the amount of laxative element, which is calcined magnesia, this powder may be made as laxative as desired. The aluminum hydroxide preparations have also seemed to give good results in one to two dram doses, their greatest disadvantage is the tendency toward constipation which sometimes follows their use. The newer magnesium trisilicate preparations, Trisomin and Trinesium, have also given very satisfactory results. Their greatest advantage is the convenience of tablet medication.

Hydrochloric Acid: In patients having an achlorhydria as demonstrated by the Ewald meal, remarkable relief may sometimes be obtained by taking a dram of dilute hydrochloric acid in orange juice with meals. Nitrohydrochloric acid, 10 minims in water, has also been advocated in these conditions. When acids are not well tolerated, one or two capsules of Acidulin may be given with meals.

Cholagogues and Choleretics: Cholagogues are substances which cause contraction of the gall bladder, primarily fats, cholesterol-containing foods and oleic acid. Choleretics are substances which will stimulate the liver to secrete more bile. The only preparations demonstrated as being of practical value in this regard are the bile salts. While there is no question about the efficacy of bile salts in stimulating bile flow, there is some question as to their therapeutic indications. Duodenal drainage studies have conclusively shown that the liver secretes with remarkable consistency a definite amount of bile salts daily. In approximately 1200 c.c. of bile secreted daily, possibly 10 grams of bile salts are discharged into the intestinal tract. A large part of this is reabsorbed and carried back to the liver, where it exerts a choleretic action. There is, therefore, probably an adequate amount of bile salts delivered by the liver under all circumstances except where there is a complete obstruction of the common duct or where liver damage has resulted in an almost complete loss of function. There is a real question whether bile salts should be administered at all under these conditions.

While bile salts are apparently beneficial in the atonic gall bladder

and in the aged suffering from constipation, contraindications to their use would seem to be hypertonic states of the biliary or intestinal tracts, duodenitis and pylorospasm. Under these conditions an increased intrahepatic pressure has been found to aggravate the discomfort of the patient, especially if antispasmodics are not given simultaneously.

Antispasmodics: With pain, colic and in the hypertonic conditions of the biliary tract, as well as in the spastic colon, the antispasmodics play a very beneficial role. Among those found very effective are atropine sulphate, extract of belladonna, tincture of belladonna, Trasentin, Syntropan and Bellergal. The three latter preparations have seemed less apt to produce dilatation of the pupils and a dry throat than the atropine preparations. Adequate doses, however, are essential to produce results in this group.

Sedatives: The highly nervous state of a large number of these patients justifies a sympathetic consideration of the individual case and the use of sedatives in as large doses as needed. The relation of nervousness and worry to symptoms has previously been discussed. The findings of a postcervical congestion, a spastic colon, and hypertonic reflexes suggest the need of sedatives. Among those which we have used with satisfactory results are phenobarbital, grains ¼ to ½; Adalin, grains 5; triple bromides, 15 grains, three times daily. Bromural and Bellergal have also been given, 1 tablet three or four times daily.

Biliary Tract Antiseptics: Although many drugs have been advocated as biliary tract antiseptics, few actually have proven to be effective in this regard. Since the only method aside from operation by which infection in the biliary tract can be actually demonstrated is by the bacterial cultures of the duodenal bile obtained under sterile precautions, the organisms must be demonstrated as being present before treatment is begun and persistently absent after treatment has been stopped. We know of no such demonstration with any drug.

On the other hand, the known excretion in the bile of certain drugs, such as neoprontosil and sulfanilamide, affords possibilities for further study. Good clinical results in the treatment of liver infection with sulfanilamide have been reported by Ottenberg.[45] Since investigations have shown that this drug is secreted in good concentration in the bile, encouragement is provided for the further study of this type of treatment.

Vaccines: The use of autogenous vaccine from the bile, stool or from foci of infection has been advocated and in use for many years by

Rehfuss.[1] We have also utilized vaccine for the past ten years and have been very well satisfied with its results in many cases. Best results are obtained if the dosage is kept very low, below the point of systemic reaction. The course of treatment, however, should be continued for at least four to six months. While there may well be some question as to the exact mechanism by which the benefit is obtained, good results are frequent in patients having this form of treatment.

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